Prostanoids Determine the Range of Cerebral Blood Flow Autoregulation of Newborn Piglets

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To assess whether prostanoids have a role in setting the blood pressure limits of cerebral blood flow autoregulation in newborn animals, we measured cerebral blood flow and prostanoid concentrations in blood from the sagittal sinus over a wide range of mean systemic blood pressures (17–117 mm Hg) in eight newborn piglets treated with 30 mg/kg i.v. ibuprofen and in eight vehicle-treated piglets. Blood pressure was adjusted by inflating balloon-tipped catheters placed at the aortic isthmus and root to induce hypertension and hypotension, respectively, 80 minutes apart in each piglet. Cerebral blood flow and concentrations of prostaglandins E and F2, 6-keto-prostaglandin F1α, and thromboxane B2 in blood from the sagittal sinus and left subclavian artery were measured 20 minutes before (baseline) and during each blood pressure adjustment. In vehicle-treated piglets, cerebral blood flow was constant at blood pressures between 50 and 90 mm Hg (r=0.06, p=0.85). When blood pressure was reduced to <50 mm Hg, thromboxane B2 concentration in the sagittal sinus increased by 597 ±42% and concentrations of the prostaglandins increased by an average of 308±45% (p<0.05). When blood pressure was raised to >90 mm Hg, concentrations of the prostaglandins increased by an average of 46 ±11%, with no change in the concentration of thromboxane B2. Treatment with ibuprofen reduced the baseline concentrations of all prostanoids and prevented their changing during hypotension and hypertension. This inhibition of prostanoid synthesis was associated with a widened range of cerebral blood flow autoregulation (blood pressures between 35 and 117 mm Hg) (r=0.26, p=0.21). In conclusion, prostaglandins and thromboxane contribute significantly to determining the blood pressure limits of cerebral blood flow autoregulation of newborn animals. (Stroke 1990;21:777–784)
rowing of their CBF autoregulatory range, predominantly at the upper limit, compared with adults. Therefore, we investigated the role of prostanoids in establishing the BP limits of CBF autoregulation in newborns. For this purpose, CBF and concentrations of PGs and TXB\textsubscript{2} in cerebral blood were measured over a wide range of systemic BPs in piglets subjected to prostanoid synthesis inhibition using ibuprofen.\textsuperscript{14}

**Materials and Methods**

This study was approved by the Animal Care and Ethics Committee of the Montreal Children's Hospital Research Institute.

We studied 16 1-3-day-old newborn piglets. They were anesthetized with halothane for catheterization of the blood vessels. The left subclavian artery was catheterized with a polyethylene umbilical vessel catheter (Argyle, 3/4 French, Sherwood, St. Louis, Missouri) for BP recording using a Statham pressure transducer (Glen Burnie, Maryland) connected to a DR-8 Electronics for Medicine recorder (White Plains, New York) and for withdrawal of blood (including reference samples). A similar catheter was placed into the left ventricle via the right subclavian artery for the injection of radiolabeled microspheres. A silicone-coated balloon-tipped catheter with fenestrations 1/2-2 cm proximal to its end (Berman Angiocath, 4 or 5 French, Arrow, Reading, Pennsylvania) was placed immediately distal to the root of the aorta via the right common carotid artery. Inflating this balloon induced hypotension in the aortic arch, and the fenestrations enabled continuous recording of aortic arch BP. A second balloon-tipped catheter was positioned in the thoracic descending aorta via a femoral artery, enabling us to induce hypertension in the aortic arch by inflating the balloon. A small polyethylene catheter (Intramedic PE-50, Becton Dickinson, Parsippany, New Jersey) was placed in the sagittal sinus via a small burr hole in the skull for blood sampling, and a second catheter was placed in a femoral vein for drug administration.

After catheterization, the piglets were allowed to recover from anesthesia under an overhead lamp for 3 1/2-4 hours. Thirty minutes before the experiment, the awake piglets were fitted comfortably on a cloth sling and placed under an infant radiant warmer to maintain their body temperature at 38°C.

During the experiment the piglets were tranquilized by breathing a prepared gas mixture of 50% N\textsubscript{2}O, 20% O\textsubscript{2}, and 30% N\textsubscript{2}, which does not affect CBF autoregulation.\textsuperscript{19} The piglets were divided randomly into two groups of eight animals each and received either 30 mg/kg i.v. ibuprofen (Sigma Chemical Co., St. Louis, Missouri) in 150 mM NaCl and 0.4N NaOH titrated to pH 7.4, a dose previously shown to inhibit cyclooxygenase efficiently, or a similar volume of vehicle (approximately 2 ml i.v.). The order in which 15-μm-diameter microspheres labeled with cerium-141, strontium-85, chromium-51, or scandium-46 (3M, Newbrighton, Minnesota) were to be injected was randomly determined. Forty minutes after treatment, the first microspheres were injected to obtain a first baseline CBF. Twenty minutes later, one balloon-tipped catheter was randomly chosen to be inflated to increase or decrease BP. Once steady-state BP was achieved (≤30 seconds after balloon inflation, as previously reported), the second microspheres were injected for CBF measurement. The balloon was slowly deflated after the injection, and the piglet was allowed to rest for 60 minutes. At the end of this rest period, the third microspheres were injected to obtain a second baseline CBF. Twenty minutes later, the other balloon-tipped catheter was inflated to obtain another desired BP and the remaining microspheres were injected for the final CBF measurement. Thus, each piglet was subjected to hypotension and hypertension induced in a random order. Mean systemic BPs were predetermined and ranged from 17 to 117 mm Hg.

CBF was measured using the radiolabeled microsphere technique previously described.\textsuperscript{21} Approximately 300,000 microspheres were injected into the left ventricle, and the catheter was flushed with 2 ml saline. Reference blood samples were withdrawn from the left subclavian artery catheter beginning 10 seconds before the injections and continuing for 70 seconds at a rate of 2 ml/min using a Harvard Apparatus infusion/withdrawal pump (South Natick, Massachusetts).

Immediately after each microsphere injection, blood samples were drawn from the sagittal sinus and left subclavian artery for the determination of blood gases, O\textsubscript{2} saturation of hemoglobin (Instrumentation Laboratories, Inc., Dayton, Ohio), concentration of hemoglobin, and concentrations of PGE, PGF\textsubscript{2α}, 6-keto-PGF\textsubscript{1α} (the stable metabolite of PGI\textsubscript{2}), and TXB\textsubscript{2} (the stable metabolite of TXA\textsubscript{2}) in the plasma. Withdrawn blood was promptly replaced with blood from a donor piglet. After the experiment each piglet was killed with pentobarbital. Autopsy was performed to verify placement of the catheters and to remove the brain.

The brain was weighed and divided into four regions: cortex, periventricular area, brainstem, and cerebellum. Radioactivity in the tissues and reference blood samples was counted in a gamma scintillation counter (Biogamma II, Beckman Instruments, Inc., Fullerton, California). Energy emitted by each radionuclide was determined by differential spectroscopy so we could subtract the percent interference among nuclides. Regional CBF in milliliters per minute per 100 g brain was calculated as (cpm per 100 g tissue × reference blood sample withdrawal rate)/cpm in reference blood sample.

Regional cerebrovascular resistance (CVR) was calculated as mean BP × regional CBF and expressed as millimeters mercury per milliliter per minute per 100 g brain. We assumed cerebral venous pressure to be negligible because sagittal sinus pressure remained constant (1-3 mm Hg). Cerebral oxygen con-
sumption was calculated as $\text{CBF} \times \text{arterial oxygen content} - \text{sagittal sinus oxygen content}$.

We have previously demonstrated in newborn piglets that concentrations of PGs in sagittal venous blood reflect local cerebrovascular PG production during the resting state and that these concentrations are similar to those in the cerebrospinal fluid. Arterial and sagittal venous blood was collected in ice-cold polypropylene tubes containing 28 mg/ml ethylenediaminetetraacetic acid and 40 µg/ml indomethacin (Sigma). The blood was immediately centrifuged at 2,450g for 15 minutes at 4°C. The plasma was stored at −70°C until PGs and TXB2 were measured by radioimmunoassay, using kits (Advanced Magnetics, Boston, Massachusetts) that have been tested for reproducibility of results.

Prostanoids were extracted with ethyl acetate, as previously described. Aliquots of plasma were assayed in duplicate. [3H]PGE, [3H]PGF2α, [3H]6-keto-PGF1α, and [3H]TXB2 were used to assay PGE, PGF2α, 6-keto-PGF1α, and TXB2, respectively. After a 2-hour incubation at 25°C, the antibody-bound analyte was separated from the unbound analyte using dextran-coated charcoal. Biofluor (New England Nuclear, Boston, Massachusetts) was used as the scintillation cocktail. The radioactive energy emitted was counted in a beta counter (Beckman). All antibodies exhibited <1.6% cross-reactivity with other prostanoids except antibodies to PGE2, which showed 100% cross-reactivity with PGE1 and PGE2. The efficiency of recovery following extraction was >90%. The interassay variability of standard curve-normalized percentage of bound tracer (B/B0) was <5%. The standards used allowed us to measure PG and TXB2 concentrations of between 20 and 20,000 pg/ml.

The data were analyzed using Student’s two-tailed paired and unpaired t tests, repeated-measures analysis of variance, comparison-among-means tests, 95% confidence intervals, linear and nonlinear correlation, and regression analysis according to analogous study protocols. Linear correlation was determined by calculating the Pearson’s product-moment correlation coefficient, r. For nonlinear correlation, Kendall’s coefficient of rank correlation, τ, was calculated. The best-fit line was determined using the least-squares method by calculating the coefficient of determination, $R^2$. For polynomial regressions, we tested the significance for each stepwise increase in the order of the polynomial function to determine whether the fit was improved. The best-fit line was that having the last sequentially entered polynomial significantly improving $R^2$. Logarithmic regression lines were also calculated according to the least-squares method after being compared with polynomial functions for best fit of the data points. Statistical significance was set at $p<0.05$. Values are expressed as mean±SEM unless otherwise specified.

### Results

Each reference blood sample contained >650 radiolabeled microspheres, and each brain region examined contained >2,500 microspheres, regardless of BP. This strongly suggested adequate mixing and distribution of the microspheres. In addition, distribution of the radiolabeled microspheres was similar in various areas of the brain as well as in the two hemispheres, which also indicated homogeneous mixing of the microspheres (compare CBF of various brain regions in Figure 1).

Arterial pH, $P_{aO_2}$, and $P_{aCO_2}$ were 7.41±0.02, 88.6±8.7 mm Hg, and 39.6±3.1 mm Hg, respectively, during the first baseline measurements in the vehicle-
FIGURE 1. Graphs of cerebral blood flow (CBF) as a function of mean systemic blood pressure (BP) in newborn piglets treated with 30 mg/kg i.v. ibuprofen (n=8, \(\triangle,-\)) or vehicle (n=8, *,-). In both vehicle- and ibuprofen-treated piglets, global (left) and regional (right) CBF was nonlinearly correlated with mean BP (\(r=0.49-0.66, p<0.001\)). For global and regional CBF, best-fit regression line was fifth-order polynomial function (\(R^2=0.75-0.87, p<0.0001\)) in vehicle-treated piglets and logarithmic function (\(R^2=0.40-0.51, p<0.005\)) in ibuprofen-treated piglets.

treated group and 7.39±0.02, 97.3±12.7 mm Hg, and 43.4±1.6 mm Hg, respectively, in the ibuprofen-treated group, and did not change significantly during the experiment in either group, as previously reported by others using analogous procedures.\(^3\)BP, CBF, and prostanoid concentrations in the sagittal sinus were similar during the first and second baseline measurements in both groups (Table 1). Baseline CBF and prostanoid concentrations were comparable to those previously reported in piglets that were not instrumented with balloon-tipped catheters.\(^9\)Global and regional CBF are plotted as a function of mean BP for the vehicle- and ibuprofen-treated piglets in Figure 1. In vehicle-treated piglets the data best fit a fifth-order polynomial function (\(R^2=0.75-0.87, p<0.0001\)), and in ibuprofen-treated piglets CBF best fit the logarithm of BP (\(R^2=0.40-0.51, p<0.005\)).

Global and regional CBF of the vehicle-treated piglets were constant between 50 and 90 mm Hg (\(r=0.07-0.36, p>0.46\)), beyond which CBF changed markedly as a function of mean BP (\(r=0.42-0.51, p<0.05\)). In contrast, in ibuprofen-treated piglets, CBF in all regions examined did not vary significantly between BPs of 35 and 117 mmHg (\(r=0.23-0.34, p=0.10-0.30\)). When BP was reduced to its lowest values (\(\leq30\) mm Hg), ibuprofen-treated piglets also exhibited a smaller decrease in CBF than vehicle-treated piglets (30±9% and 75±4%, respectively, \(p<0.01\)). Global and regional CBF during baseline conditions were similar in the two groups (Figure 1, Table 1). The only regional difference during baseline conditions for either group was observed in the periventricular area, which exhibited a lower CBF than the other regions (\(p<0.05\), Table 1).

Global and regional CVR (Figure 2) in vehicle-treated piglets correlated linearly with BP in the range 50–90 mm Hg (\(r=0.54–0.78, p<0.05\)), beyond which it was independent of BP (\(r=0.30–0.03, p=0.29–0.93\)). In contrast, CVR in the ibuprofen-treated piglets was linearly related to mean BP over the entire range studied, 17–117 mm Hg (\(r=0.84–0.96, p<0.0001\)). In addition, the slopes of these regression lines were steeper than those of the vehicle-treated group for the cortex and periventricular area in the BP range 50–90 mm Hg. Thus, the data demonstrate that ibuprofen enhanced CBF autoregulation.

Ibuprofen treatment did not alter the relation between cerebral oxygen consumption and BP, which were correlated as a second-order polynomial function in both groups (vehicle-treated: \(r=0.48, p<0.01\); ibuprofen-treated: \(r=0.56, p<0.01\)).

Concentrations of prostanoids during changes in BP are shown in Table 2. In the vehicle-treated piglets, during hypotension (BP below the range of CBF autoregulation, 17–49 mm Hg) in the sagittal sinus there was a significant increase in the concentrations of PGE\(_2\), PGF\(_2\alpha\), 6-keto-PGF\(_1\alpha\), and TXB\(_2\), which all varied inversely as a function of BP (\(r=-0.87 to -0.98, p<0.0001\)) and consequently of global CBF (\(r=-0.68 to -0.89, p<0.05\)). TXB\(_2\) exhibited the highest percentage increase, 597±42%, with smaller increases (\(p<0.05\)) for PGE, PGF\(_2\alpha\), and 6-keto-PGF\(_1\alpha\), of 349±51%, 327±51%, and 303±41%, respectively. In contrast, during hypertension (BP above the range of CBF autoreg-
ulation, 91–117 mm Hg), in the sagittal sinus there was a BP-dependent increase in the PG concentrations ($r=0.58-0.77$, $p<0.05$), which averaged $46\pm11\%$, without any associated changes in TXB$_2$ concentration.

In the ibuprofen-treated piglets the sagittal sinus concentrations of PGE, PGF$_{2\alpha}$, 6-keto-PGF$_{1\alpha}$, and TXB$_2$ were lower than those in the vehicle-treated piglets ($p<0.001$). There were no changes in prostanoid concentrations in the sagittal sinus during hypotension or hypertension in the ibuprofen-treated piglets (Table 2).

Prostanoid concentrations in the arterial blood of vehicle-treated piglets were lower than those in the sagittal sinus blood ($p<0.01$). This reflects local cerebrovascular prostanoid production, as we have previously reported.9

Discussion

Our data indicate that prostanoids have a significant role in determining the BP limits of CBF autoregulation of newborn animals. Our observations in this study are consistent with findings in our and other laboratories,3,5,9,11,13,14,24,28–33 suggesting that the experimental protocol was reliable. We used balloon-tipped catheters to change systemic BP instead of pharmacologic agents, which may produce direct cerebrovascular effects. As indicated in “Materials and Methods,” the number of microspheres detected in all reference blood samples and brain tissues were highly suggestive of adequate mixing of microspheres.21 Furthermore, our cerebral hemodynamic findings in vehicle-treated piglets are similar to those in fetal lambs subjected to a similar protocol.3

Since cerebrovascular autoregulatory responses occur very rapidly (within 10 seconds),18 we measured CBF once the desired BP reached a steady state, as previously described for fetal lambs.3 However, prostanoid concentrations may have been changing when CBF was measured. Prostanoid synthesis is a dynamic process that occurs during physiologic alterations.16,17,34 Prostanoid concentrations in the brain change during ischemia.31–35 Nonetheless, ample evidence from studies in adult animals suggests that during ischemia, the changes in prostanoid concentrations in the brain account for the cerebrovascular events.11,13,14,29–30 In addition, it appeared to be appropriate to relate changes in cerebrovascular prostanoid concentrations to CBF autoregulation by concomitantly measuring CBF and prostanoid concentrations in the sagittal sinus as a function of BP. Most importantly, the widening of the CBF autoregulatory range produced by ibuprofen was consistent with the changes in prostanoid concentrations in the vehicle-treated piglets (Table 2).

In vehicle-treated piglets, hypotension resulted primarily in a marked increase in cerebrovascular concentrations of the most potent prostanoid, TXA$_2$ (which we measured as TXB$_2$) (Table 2), a cerebral vasoconstrictor13,17 that is equally effective and potent in young and older animals.36 These elevated levels of TXA$_2$ at low BPs may have counteracted the cerebral vasodilatory actions of PGE, PGF$_{2\alpha}$, and PGI$_2$ (measured in our study as 6-keto-PGF$_{1\alpha}$) in the newborn piglets.6,8 This inference is supported by our
TABLE 2. Concentrations of Prostanoids in Arterial and Sagittal Sinus Blood in Vehicle- and Ibuprofen-Treated Piglets During Normotension, Hypotension, and Hypertension

<table>
<thead>
<tr>
<th>Prostanoid</th>
<th>Hypotension  (17-49 mm Hg)</th>
<th>Normotension (50-90 mm Hg)</th>
<th>Hypertension (91-117 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sagittal sinus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle-treated (n=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGE</td>
<td>6,762±343*</td>
<td>1,549±46</td>
<td>2,406±111†</td>
</tr>
<tr>
<td>PGF_{2α}</td>
<td>1,043±101*</td>
<td>263±21</td>
<td>414±48†</td>
</tr>
<tr>
<td>6-keto-PGF_{1α}</td>
<td>2,391±268*</td>
<td>611±25</td>
<td>776±72†</td>
</tr>
<tr>
<td>TXB_{2}</td>
<td>669±48*</td>
<td>96±9</td>
<td>108±7</td>
</tr>
<tr>
<td>Ibuprofen-treated (n=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGE</td>
<td>449±26†</td>
<td>436±18†</td>
<td>470±25†</td>
</tr>
<tr>
<td>PGF_{2α}</td>
<td>31±7†</td>
<td>26±2†</td>
<td>24±3†</td>
</tr>
<tr>
<td>6-keto-PGF_{1α}</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TXB_{2}</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td><strong>Artery</strong></td>
<td></td>
<td></td>
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<tr>
<td>Vehicle-treated (n=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGE</td>
<td>297±16*§</td>
<td>107±6§</td>
<td>160±11†§</td>
</tr>
<tr>
<td>PGF_{2α}</td>
<td>348±23*§</td>
<td>146±8§</td>
<td>194±19§</td>
</tr>
<tr>
<td>6-keto-PGF_{1α}</td>
<td>417±23*§</td>
<td>203±6§</td>
<td>285±28§</td>
</tr>
<tr>
<td>TXB_{2}</td>
<td>317±24*§</td>
<td>106±15</td>
<td>165±21†§</td>
</tr>
</tbody>
</table>

PG, prostaglandin; TX, thromboxane; —, undetectable, concentration of <20 pg/ml. Prostanoid concentrations in arterial blood of ibuprofen-treated piglets were all <20 pg/ml. Values are mean±SEM pg/ml.

*<p<0.01 different from normotension and hypertension by analysis of variance for repeated measures.
†<p<0.05 different from normotension by analysis of variance for repeated measures.
‡<p<0.001 different from sagittal sinus in vehicle-treated by unpaired t test.
§<p<0.01 different from vehicle-treated by unpaired t test.

Findings with ibuprofen, which markedly inhibited prostanoid synthesis, achieving undetectable levels of TXB_{2} (Table 2). This inhibition was associated with an extension of the lower BP limit of CBF autoregulation, from 50 to approximately 35 mm Hg, and an attenuation in the decrease in CBF below this BP (Figure 1). Thus, the increases in TXB_{2} concentration when BP was reduced below the lower limit of CBF autoregulation (50 mm Hg) seem to contribute in setting the lower limit of CBF autoregulation in newborn piglets. These findings are in accord with those of studies in adult animals that suggest a contribution for TXA_{2} in cerebral ischemia following hypotension and a reduction in cerebral perfusion pressure.11,13-15,37,38

On the other hand, during hypertension increases in the concentrations of the neonatal vasodilators PGE, PGF_{2α}, and PGI_{2}8,9 without changes in the concentration of the constrictor TXA_{2} in vehicle-treated piglets (Table 2) may have contributed to restricting the upper limit of CBF autoregulation in newborn piglets to a BP of 90 mm Hg. This suggestion was strengthened by inhibiting prostanoid synthesis, which prevented the rise in the concentrations of PGs during hypertension. Cyclooxygenase inhibition was associated with a progressive increase in CVR as BP rose (Figure 2), extending the upper limit of CBF autoregulation to the highest BP studied, 117 mm Hg (Figure 1). Enhancement of CBF autoregulation at the upper BP limit in ibuprofen-treated piglets is particularly relevant for the periventricular area and may account for the prevention of intraventricular hemorrhages observed with indomethacin.4,39,40

In distinction to our data with ibuprofen, Pickard et al41 found that indomethacin did not alter CBF autoregulation in adult baboons. These workers increased BP with angiotensin, a cerebral vasoconstrictor,42 and their changes in BP remained within the range of CBF autoregulation. Moreover, there may be differences between indomethacin and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen.9,10,20,34,43

Ibuprofen did not alter baseline CBF. This contrasts with the decrease in CBF produced by indomethacin.4-6,9 However, recently we9,10 and other investigators11,12,20,43 have suggested that indomethacin exerts its vascular effects independent of cyclooxygenase inhibition, in contrast to other NSAIDs such as ibuprofen.10,20,34,44 In human infants, indomethacin also decreases cerebral blood velocity ≤15 minutes after its administration,45 before any changes in cerebral prostanoid concentration are known to occur.46 Indomethacin possesses several actions other than cyclooxygenase inhibition47-49 that may account for the CBF reduction described during a BP decrease within the limits of CBF autoregulation in newborn animals. Thus, these studies suggest that there are differences in the cerebrovascular action of indomethacin and other NSAIDs. In a recent review on prostanoids, Oates et al84 concluded that prostanoids act predominantly as mediators of adaptive responses, as suggested in our study.
In conclusion, our findings indicate that PGs and TXA2 play a significant role in determining the range of CBF autoregulation of newborn animals. The marked increases in cerebrovascular concentrations of the constrictor TXA2 when BP is reduced to below the lower limit of CBF autoregulation and the marked increases in cerebrovascular concentrations of the neonatal cerebral vasodilators PGE, PGF\(_{2\alpha}\), and PGF\(_{3\alpha}\) when BP is increased above the upper limit of autoregulation may contribute to setting the BP range of CBF autoregulation in newborn animals, which is narrowed predominantly at its upper limit compared with adults. Inhibition of prostanoid synthesis resulted mostly in an extension of the upper limit of CBF autoregulation. We propose that differences between the CBF autoregulatory BP ranges of newborn and adult animals result, at least in part, from differences in the effects of PGs on the cerebral circulation of these two groups.\(^5\),\(^9\),\(^51\) PGE\(_1\) and PGF\(_{3\alpha}\) primarily increase CBF in newborns,\(^9\) whereas they reduce CBF in adults of almost all species.\(^16\),\(^17\) Finally, in the therapeutic setting, extension of the BP range of CBF autoregulation using the cyclooxygenase inhibitor ibuprofen may provide potential leads for the development of pharmacologic modes to prevent the hemorrhagic and ischemic encephalopathies of newborns.

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